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Synthesis, NMR Characterization, and a Simple Application of Lithium Borotritide

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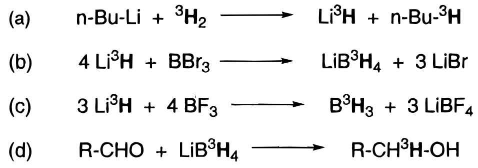
$LiBH_4$ is a powerful and selective reagent for regiospecific reduction reactions. A simple synthesis of LiB^3H_4 at near theoretical specific radioactivity is reported. We have treated Li^3H synthesized from tritium gas ($^3H_2$, ~98%) with BBr_3 to produce LiB^3H_4 (specific activity = 4120 GBq/mmol = 110 Ci/mmol. The maximum theoretical specific activity of LiB^3H_4 is 4252 GBq/mmol = 115.04 Ci/mmol; 1 matom of ^3H = 1063 GBq = 28.76 Ci.) The tritium labeling performance of the reagent was tested by an exemplary reduction of 2-naphthaldehyde to 2-naphthalenemethanol. LiB^3H_4 and the reduction products were characterized by a combination of ^1H, ^3H, and ^{11}B NMR techniques, as appropriate.

Introduction

LiB^3H_4 of high specific radioactivity is readily synthesized from the reaction of Li^3H (Scheme 1a)[1] with BBr_3 (Scheme 1b). The synthesis is very similar to that of the tritiated borane−THF complex,[2] with choice of appropriate conditions and stoichiometry to yield borohydride rather than borane (*cf.* Scheme 1b to 1c). $LiBH_4$ is often considered an analogue of $NaBH_4$, but in an ether or THF medium, the Li^+ cation is a stronger Lewis acid than the Na^+ cation, and this endows $LiBH_4$ with increased reducing power over that of $NaBH_4$.[3] $NaBH_4$ has been used as a selective reducing agent for aldehydes, ketones, and acid chlorides[4−6] and for the reductive displacement of primary and secondary alkyl halides, sulfonate esters, tertiary amines, and disulfonimides.[7] In addition to this chemistry, $LiBH_4$ reduces esters and lactones without affecting acids, amides, nitriles, or NO_2 groups.[8,9] In combination with other reagents, $LiBH_4$ is capable of reducing epoxides, acids, tertiary amides, and nitriles, while sulfones, sulfoxides, and NO_2 groups remain untouched.[9]

With these properties, LiB^3H_4 is obviously valuable in tritium-labeling reactions since it (i) is a regioselective labeling reagent; (ii) is a stronger reagent than $NaBH_4$ but possesses much greater selectivity than $LiAlH_4$, especially for the reduction of esters in the presence of other reducible groups;[10] (iii) is a very efficient reagent for the conversion of lactones in the synthesis of labeled carbohydrates;[11] (iv) is readily soluble in a wide range of solvents such as alcohols and ethers[3] so that homogeneous reductions are possible; and (v) has a higher (R) diastereoselectivity than $NaBH_4$ and KBH_4, and thus synthesis of chiral biological products can be readily achieved through diastereoselective reduction.[12]

Scheme 1. Preparation and Use of LiB^3H_4[a]



[a] (a) Synthesis of Li^3H. Reaction conditions: 1.1 mol TMEDA, hexanes as the solvent, 1 h at rt; (b) Synthesis of LiB^3H_4 from Li^3H. Reaction conditions: THF as the solvent, addition of BBr_3 at 0 °C, 15 min at 0 °C, 30 min at 70 °C; (c) Synthesis of the B^3H_3−THF complex from Li^3H. Reaction conditions: THF as the solvent, 1 h at 70 °C; (d) Reduction of an aldehyde with LiB^3H_4. Reaction conditions: THF as the solvent, 2 h at rt.

There are numerous reports on the synthesis of $LiBH_4$, most of which are impractical on a small scale or for the preparation of a highly tritiated material. In the early work, $LiBH_4$ was synthesized from the reaction between LiC_2H_5 and diborane or $Al(BH_4)_3$.[13] $LiBH_4$ can be prepared from LiH by treatment with $B(OCH_3)_3$, but extraction of the product from the crude reaction is difficult.[14] $NaBH_4$ can also be converted to $LiBH_4$ by treatment with LiBr or LiCl.[15,16]

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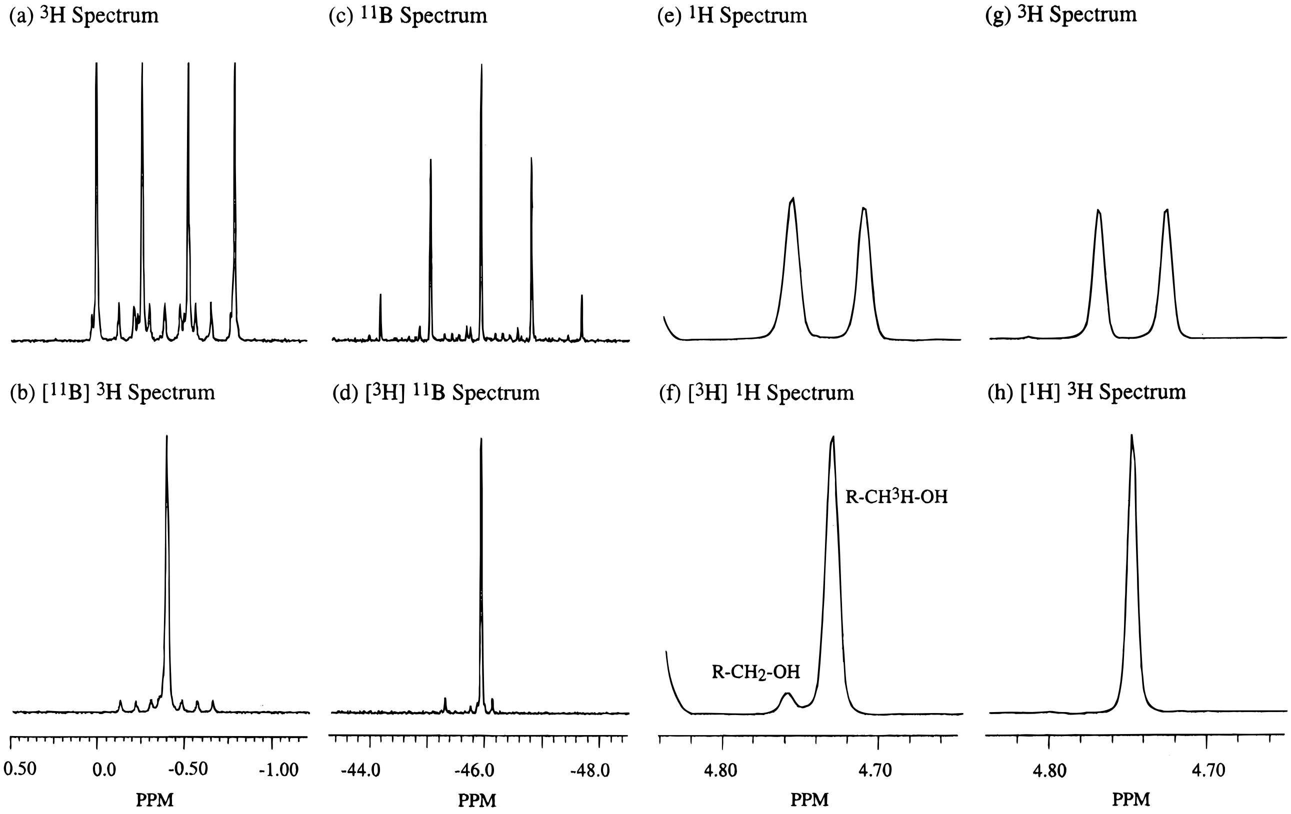

Figure 1. NMR spectra of LiB^3H_4 in $NaOH/CD_3OD$ (a−d): (a) 320 MHz ^3H spectrum (0.5 to −1.2 ppm); (b) selective ^{11}B-decoupled ^3H NMR spectrum; (c) 96 MHz ^{11}B NMR spectrum (−43.3 to −48.5 ppm); (d) ^3H-decoupled ^{11}B spectrum. NMR spectra (4.84 − 4.65 ppm) of 2-naphthalenemethanol in CD_3OD (e−h): (e) 300 MHz ^1H NMR spectrum; (f) ^3H-decoupled ^1H NMR spectrum; (g) 320 MHz ^3H NMR spectrum; (h) ^1H-decoupled ^3H NMR spectrum.

Hydrogen isotope labeled $LiBH_4$ may be prepared by the reaction of labeled diborane with LiC_2H_5,[13] LiH,[17] or $LiOC_2H_5$.[17] The rapid exchange of ^2H_2O or tritiated water with $LiBH_4$ has been reported, but after the exchange was complete, 50% of the borohydride had been hydrolyzed.[18,19] LiB^2H_4 was prepared[20] from $(CH_3)_3N{:}B^2H_3$ and $LiOCH_3$, but it was difficult to obtain a pure product. Tritiated $LiBH_4$ with a low tritium content was prepared by simply heating the solid with a mixture of H_2 and T_2 gas.[21] Our recent experience[22] with this exchange method for $LiBH_4$ suggests that borohydride with 70−75% of the theoretical tritium content is routinely available but that it is impractical to pursue material with a higher specific activity by this approach. In addition, we believe that heat treatment of the borohydride reduces its chemical reactivity.

The most convenient one-pot synthesis of $LiBH_4$ is the reduction of boron halide by lithium hydride.[23,24] It is also the most successful method in preparing LiB^2H_4, with a reported yield of 57% and 98−99% D.[20] As expected from the reactions in Scheme 1, our investigations into the preparation of the tritiated borane−THF complex (Scheme 1c)[2] sometimes yielded LiB^3H_4,[25] but the reagent was not well characterized and was never used in reduction reactions. With our ability to make finely divided and highly reactive Li^3H[1,26] and our recent experience with borane synthesis,[2] we made the production of LiB^3H_4 with high specific activity our focus. Our goal was to develop a routine synthesis of LiB^3H_4, characterize it by NMR spectroscopy, and study the products of some simple reduction reactions (Scheme 1d).

Results and Discussion

Initial investigations were carried out using deuterium gas to demonstrate the synthesis of LiB^2H_4 from Li^2H, prior to any tritium experiments. In these early studies, it became clear from the ^{11}B NMR analyses that Li^2H reduction of BBr_3 gave a higher yield of LiB^2H_4 (75%) than the Li^2H reduction of BF_3 (<50%). Calculation of the stoichiometry and the yields assumed quantitative formation of Li^2H from *n*-BuLi. Once the synthetic protocol was established, a sample of LiB^3H_4 was prepared for NMR study and use in an exemplary reaction. The LiB^3H_4 yield was assumed to be 75% based on the preliminary deuterium experiments. The full experimental details of NMR studies analogous to those described below have appeared elsewhere.[2,22]

NMR Characterization of Lithium Borotritide. The ^{10}B- and ^{11}B-coupled 320 MHz ^3H NMR spectrum obtained from LiB^3H_4 is shown in Figure 1a. The pattern

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is centered at $\delta = -0.40$ ppm and consists of an intense quartet [$J(^3H-^{11}B) = 84.5$ Hz] due to ^{11}B coupling ($I = ^3/_2$, 80.42%) that is superimposed on a weaker septet [$J(^3H-^{10}B) = 28.3$ Hz] due to ^{10}B coupling ($I = 3$, 19.58%). The observed chemical shift and coupling constants [$J(^3H-^{11}B)$, $J(^3H-^{10}B)$] are similar to published data.[22,27,28] A weak and unresolved quartet of doublets attributable to $Li^{11}BH^3H_3$ was also observed at the base of the main quartet. Selective irradiation of ^{11}B leads to the collapse of both the $Li^{11}B^3H_4$ and $Li^{11}BH^3H_3$ quartets to give the large singlet and downfield shoulder shown in Figure 1b. The $Li^{10}B^3H_4$ septet is unaffected by the irradiation and is clearly observed with the central line obscured by the singlets from the ^{11}B species. The ^{11}B NMR spectra of the same LiB^3H_4 sample are shown in Figure 1c,d. The ^1H- and ^3H-coupled ^{11}B spectrum in Figure 1c shows a quintet centered at $\delta = -45.9$ ppm (reference: $BF_3{\cdot}OEt_2$ in THF = 0 ppm). The observed splitting is dominated by the most abundant coupling partner (^3H) and the approximate $J(^3H-^{11}B) = 84.5$ Hz. The other weak multiplets are attributable to the ^1H- and ^3H-coupled ^{11}B signals from $LiBH^3H_3$. When ^3H was decoupled from ^{11}B (Figure 1d), a singlet attributable to LiB^3H_4 with the measured intensity of 87.6% and a small doublet attributable to $LiBH^3H_3$ (12.4%) were observed. There is a small unassigned single peak at *ca.* −45.8 ppm. No ^{11}B signals arising from $LiBH_2{}^3H_2$, $LiBH_3{}^3H$, and $LiBH_4$ isotopomers were detected, and this suggests that the product has a very high tritium incorporation (calculated 96.9%). Calculation of the deuterium content in LiB^2H_4 from the ^{11}B NMR of an analogous deuterium synthesis gave 98.2% D. The isotope effect ($\Delta\delta = 0.218 \pm 0.003$ ppm at 96.28 MHz) on the ^{11}B chemical shift induced by ^3H substitution is readily measured from the spectrum in Figure 1d. This value compares well with the literature values for the ^2H primary isotope effects on ^{11}B chemical shifts.[27,28]

Reduction Using Lithium Borotritide. The rest of the reagent stock solution (*ca.* 350 μL) was used for the reduction of 2-naphthaldehyde to 2-naphthalenemethanol (Scheme 1d). The product was isolated[22] and analyzed by radio-HPLC followed by both ^1H and ^3H NMR spectroscopy. In comparable deuterium reactions, deuterated products were analyzed by ^1H and ^2H NMR spectroscopy, HPLC, and mass spectrometry.

HPLC analysis of the reduction product, 2-naphthalenemethanol, showed that the chemical yield was high (89%) and that essentially all of the radioactivity was in the desired labeled product. Estimates of the specific activity were made by liquid scintillation counting of the isolated HPLC peak effluent (910 GBq/mmol, 86% of the theoretical value) and by analysis of NMR spectra. The 300 MHz ^1H NMR spectra of the reduction product are shown in Figure 1e,f. The ^3H-coupled ^1H spectrum in Figure 1e shows a doublet [$J(^1H-^3H) = 13.90$ Hz] due to the $^1H-^3H$ coupling in the singly tritiated $R-CH^3H-OH$ species. One peak of the doublet is taller than the other because it is superimposed on a small singlet from the $R-CH_2-OH$ species. The doublet collapsed into a singlet with double the intensity when ^3H was selectively irradiated (Figure 1f). The tritium isotope shift ($\Delta\delta$) was measured as 0.031 ± 0.002 ppm. Calculation of the specific activity from the peak integrals in Figure 1f gives a value of 1020 GBq/mmol (96.2% of the theoretical maximum of 1063 GBq/mmol), which is very close to the available tritium in the reagent LiB^3H_4 (96.9%) as determined from the ^{11}B NMR spectra (Figure 1d). It is not clear why there is such a large disparity between the HPLC and NMR results for the specific activity (86 vs 96% tritium). The two methods have entirely different bases, with the HPLC approach combining data from a small measured mass (compared to an appropriate standard) and a large measured radioactivity to yield the specific activity. In contrast, the NMR approach uses only the measured integral (or intensity) of the relevant isotopomers to project the specific activity and makes no assumptions about chemical purity or standardization.

The 320 MHz (^1H-coupled) ^3H NMR spectrum in Figure 1g shows a doublet from the $R-CH^3H-OH$ species. As expected, this doublet collapsed to a singlet when ^1H was irradiated (Figure 1h). The observed coupling constant [$J(^1H-^3H) = 13.81$ Hz] matches previous observations.[2,22] The product NMR spectra shown in parts e−h of Figure 1 were very clean and showed minimal levels of byproducts.

Conclusions

With the development of hydride reducing chemistry over the last 60 years, $NaBH_4$ and $LiAlH_4$ have been the most widely used reagents. NaB^3H_4[22] and $LiAl^3H_4$[29] can be prepared at *ca.* 75% and >95% of the maximum theoretical tritium content, respectively, and reductive tritiation reactions have relied heavily on the use of these two reagents, despite their known limitations.[5] $LiAlH_4$ is an exceedingly powerful reagent, capable of reducing many organic functional groups, but is of little value for selective reductions. $NaBH_4$ is too mild to achieve efficient reductions for some functional groups, *e.g.*, epoxides, esters, and lactones. $LiBH_4$ has a reactivity that is intermediate between those two extremes,[5,30] with a reducing power which can be easily modified using catalysts.[30−33] These properties give access to a wide spectrum of selective reductions, and consequently, specific labeling.

We have demonstrated the synthesis and use of highly deuterated or tritiated $LiBH_4$ on a microscale with a yield of *ca.* 75%. ^3H and ^{11}B NMR analysis of LiB^3H_4 showed close to 100% tritium content. Both the ^2H and ^3H reagents smoothly reduced 2-naphthaldehyde to the corresponding alcohol and gave regiospecific labeling, excellent yields (*ca.* 90%), and very high isotope abundances (≥96% for tritium). The reagents may be prepared and reductions commenced in less than 3 h in a simple reaction apparatus. The simple synthesis of LiB^2H_4 and LiB^3H_4, neither of which is commercially available, should open the door to a new phase of regioselective tritium and deuterium labeling chemistry. In addition to the simple aldehyde reduction presented here, our experience with LiB^3H_4 has included the complete reduction of an acid chloride to $R\text{-}C^3H_2\text{-}OH$ in

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the presence of an aryl halide[34] and the stereoselective reduction of a ketone in the presence of a secondary amide.[35]

Experimental Section

General. Very similar materials and analytical methods were recently reported for the preparation of the tritiated borane−THF complex.[2] BBr_3 (1.0 M solution in hexanes) was used as purchased from Aldrich Chemical Co. All NMR analyses (^1H, ^2H, ^3H, and ^{11}B) were performed on a Bruker AC-300 NMR spectrometer.

Lithium Borotritide Synthesis. As previously described,[2] 0.4 mmol of Li^3H was prepared in a 5 mL round bottom flask with a side arm having a septum inlet. After the Li^3H was dried under vacuum for 1 h, dry nitrogen gas was introduced into the flask to a pressure of 80 kPa and tetrahydrofuran (THF, 650 μL) was added. The flask was cooled using a 0 °C ice bath, and BBr_3 (0.1 mmol, 100 μL of 1.0 M solution in hexanes) was injected dropwise into the flask. After the solution was stirred at 0 °C for 15 min, it was refluxed at 70 °C with constant stirring for 30 min. One aliquot (300 μL) was withdrawn from the flask to be used in another reduction reaction,[34] and a second aliquot (80 μL) was taken for NMR study. The solvents were evaporated from the small aliquot, the residue was dissolved in $NaOH/CD_3OD$ (400 μL, saturated solution), and the solution was transferred into a Teflon tube for NMR study. Full descriptions of analogous NMR studies have appeared elsewhere.[2,22] The LiB^3H_4 yield was assumed to be 75% based on preliminary deuterium experiments.

Lithium Borotritide Reduction of Naphthaldehyde. A solution of 2-naphthaldehyde (4.7 mg, 0.03 mmol in 225 μL of CH_3OH) was injected into a flask containing the residual solution of LiB^3H_4 (0.035 mmol in *ca.* 350 μL of THF/hexanes, 96.9% ^3H, 145 GBq = 3.9 Ci) and stirred at room temperature. After 2 h of stirring, the reaction was quenched by addition of CH_3OH (300 μL). The reduction product was isolated[22] and analyzed by radio-HPLC followed by both ^1H and ^3H NMR spectroscopy. In comparable deuterium reactions, the deuterated products were analyzed by ^1H and ^2H NMR spectroscopy, HPLC, and mass spectrometry, which allowed calculation of the deuterium content (% D) in the molecule. Deuterium experiment: yield 95%; 80% D; MS *m/z* 160 (9.9), 159 (72.9), 158 (17.2); ^2H NMR (CH_3OH, ^1H-decoupled) δ 4.74 (CH^2H). Tritium (98%) experiment: yield 89%; specific activity (by HPLC) 910 GBq/mmol, (by 300 MHz ^1H NMR, CD_3OD, ^3H-decoupled) 1020 GBq/mmol; ^1H NMR (CD_3OD, ^3H-decoupled) δ 4.80 (CH_2, 7.2%), 4.75 (CH^3H, 92.8%); ^3H NMR (CD_3OD, ^1H-decoupled) δ 4.75 (CH^3H, 100%).

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Note Added in Proof. A further example of the use of LiB^3H_4 with high specific activity was recently published: Huguenin, P. N.; Shimma, N. *J. Labelled Compd. Radiopharm.* **1996**, *38*, 999−1005.

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